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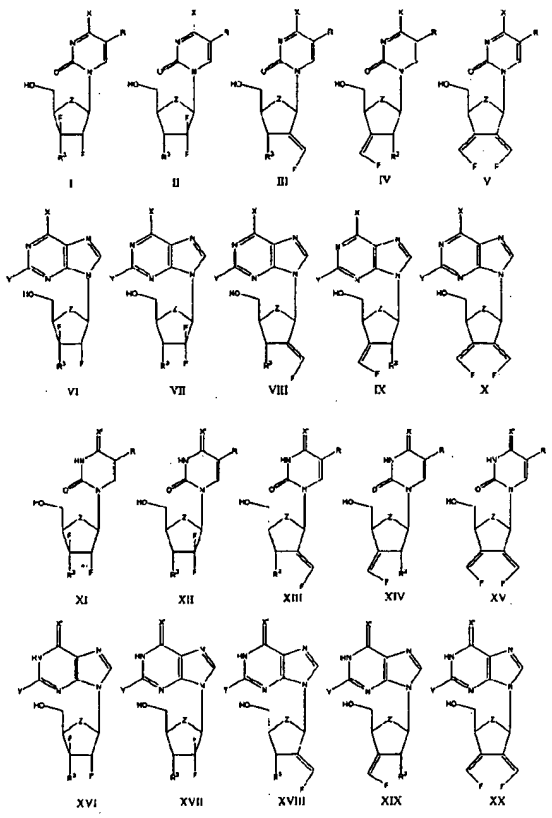

(57) Abstract: The invention is a compound, composition, use for and a method of treating *Flaviviridae* (Hepacivirus, Flavirius, Pestivirus) infections, including BVDV and HCV, or abnormal cellular proliferation, including malignant tumors, in a host including animals, and especially humans, using a ß-D or ß-L nucleoside of general formula (1) - (XX), or their pharmaceutically acceptable salt or prodrug thereof.

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MODIFIED FLUORINATED NUCLEOSIDE ANALOGUES

FIELD OF THE INVENTION

The present invention includes compounds and methods for the treatment of *Flaviviridae* infections, such as bovine viral diarrhea virus ("BVDV"), Dengue Virus (DENV), West Nile Virus (WNV) and hepatitis C virus (HCV) as well as abnormal cellular proliferation.

This application claims priority to U.S. provisional application number 60/357,411, filed on February 14, 2002, and U.S. serial number 60/358,140, filed on February 20, 2002.

BACKGROUND OF THE INVENTION

Flaviridídae

The *Flaviviridae* is a group of positive single-stranded RNA viruses with a genome size from 9-15 kb. They are enveloped viruses of approximately 40-50 nm. An overview of the *Flaviviridae* taxonomy is available from the International Committee for Taxonomy of Viruses. The *Flaviviridae* consists of three genera.

1. Flaviviruses. This genus includes the Dengue virus group (Dengue virus, Dengue virus type 1, Dengue virus type 2, Dengue virus type 3, Dengue virus type 4), the Japanese encephalitis virus group (Alfuy Virus, Japanese encephalitis virus, Kookaburra virus, Koutango virus, Kunjin virus, Murray Valley encephalitis virus, St. Louis encephalitis virus, Stratford virus, Usutu virus, West Nile Virus), the Modoc virus group, the Rio Bravo virus group (Apoi virus, Rio Brovo virus, Saboya virus), the Ntaya virus group, the Tick-Borne encephalitis group (tick born encephalitis virus), the Tyuleniy virus

group, Uganda S virus group and the Yellow Fever virus group. Apart from these major groups, there are some additional Flaviviruses that are unclassified.

2. Pestiviruses. This genus includes Bovine Viral Diarrhea Virus-2 (BVDV-2), Pestivirus type 1 (including BVDV), Pestivirus type 2 (including Hog Cholera Virus) and Pestivirus type 3 (including Border Disease Virus).

3. Hepaciviruses. This genus contains only one species, the Hepatitis C virus (HCV), which is composed of many clades, types and subtypes.

One of the most important *Flaviviridae* infections in humans is caused by the hepatitis C virus (HCV). This is the second major cause of viral hepatitis, with an estimated 170 million carriers world-wide (World Health Organization; *Hepatitis C: global prevalence*, Weekly Epidemiological Record, **1997**, *72*, 341), 3.9 million of whom reside in the United States (Centers for Disease Control; unpublished data, http://www.cdc.gov/ncidod/diseases/ hepatitis/heptab3.htm). Chronic infection with HCV can lead to liver inflammation, cirrhosis, cancer and death.

The genomic organization of the *Flaviviridae* share many common features. The hepatitis C virus (HCV) genome is often used as a model. HCV is a small, enveloped virus with a positive single-stranded RNA genome of ~9.6 kb within the nucleocapsid. The genome contains a single open reading frame (ORF) encoding a polyprotein of just over 3,000 amino acids, which is cleaved to generate the mature structural and nonstructural viral proteins. The ORF is flanked by 5' and 3' non-translated regions (NTRs) of a few hundred nucleotides in length, which are important for RNA translation and replication. The translated polyprotein contains the structural core (C) and envelope proteins (E1, E2, p7) at the N-terminus, followed by the nonstructural proteins (NS2, NS3, NS4A, NS4B, NS5A, NS5B). The mature structural proteins are generated via cleavage by the host signal peptidase (*see*: Hijikata, M. *et al.* Proc. Nat. Acad. Sci., USA, **1991**, *88*, 5547; Hussy, P. *et al.* Virology, **1996**, *224*, 93; Lin, C. *et al.* J. Virol., **1994**, *68*, 5063; Mizushima, H. *et al.* J. Virol., **1994**, *68*, 2731; Mizushima, H. *et al.* J. Virol., **1994**, *68*, 6215; Santolini, E. *et al.* J. Virol., **1994**, *68*, 3631; Selby, M. J. *et al.* Virology, **1994**, *204*, 114; and Grakoui, A. *et al.* Proc. Nat. Acad. Sci., USA, **1993**, *90*, 10538). The junction between NS2 and NS3 is autocatalytically cleaved by the NS2/NS3 protease (*see*: Hijikata, M. *et al.* J. Virol., **1993**, *67*, 4665 and Bartenschlager, R. *et al.* J. Virol., **1994**, *68*, 5045),

while the remaining four junctions are cleaved by the N-terminal serine protease domain of NS3-complexed with NS4A (*see*: Failla, C. *et al.* J. Virol., **1994**, *68*, 3753; Lin, C. *et al.* J. Virol., **1994**, *68*, 8147; Tanji, Y. *et al.* J. Virol., **1995**, *69*, 1575 and Tai, C. L. *et al.* J. Virol., **1996**, *70*, 8477). The NS3 protein also contains the NTP-dependent helicase activity which unwinds duplex RNA during replication. The NS5B protein possesses *RNA-dependent RNA polymerase* (RDRP) activity (*see*: Behrens, S. E. *et al.* EMBO J., **1996**, *15*, 12; Lohmann, V. *et al.* J. Virol., **1997**, *71*, 8416-8428 and Lohmann, V. *et al.* Virology, **1998**, *249*, 108), which is essential for viral replication (Ferrari, E. *et al.* J. Virol., **1999**, *73*, 1649). It is emphasized here that, unlike HBV or HIV, no DNA is involved in the replication of HCV. Recently *in vitro* experiments using NS5B, substrate specificity for HCV-RDRP was studied using guanosine 5'-monophosphate (GMP), 5'-diphosphate (GDP), 5'-triphosphate (GTP) and the 5'-triphosphate of 2'-deoxy and 2',3'-dideoxy guanosine (dGTP and ddGTP, respectively). The authors claimed that HCV-RDRP has a strict specificity for ribonucleoside 5'-triphosphates and requires the 2'- and 3'-OH groups (Lohmann; Virology, 108).

Dengue Virus (DENV) is the causative agent of Dengue Hemorrhagic Fever (DHF). According to the world Health Organization (WHO), two fifths of the world population are now at risk for infection with this virus. An estimated 500,000 cases of DHF require hospitalization each year with a mortality rate of 5% in children.

West Nile Virus (WNV), a flavivirus previously known to exist only in intertropical regions, has emerged in recent years in temperate areas of Europe and North America, presenting a threat to public health. The most serious manifestation of WNV infection is fatal encephalitis in humans. Outbreaks in New York City and sporadic occurrences in the Southern United States were reported since 1999.

Examples of antiviral agents that have been identified as active against the Flaviviridae family of viruses include:

(1) interferon and ribavirin (Battaglia, A.M. *et al.*, *Ann. Pharmacother*, **2000**, *34*, 487-494); Berenguer, M. *et al. Antivir. Ther.*, **1998**, *3* (Suppl. 3), 125-136).

Ribavirin (1-β-D-ribofuranosyl-1-1,2,4-triazole-3-carboxamide) is a synthetic, non-interferon-inducing, broad spectrum antiviral nucleoside analog. It is sold under the

trade names Virazole™ (The Merck Index, 11th edition, Editor: Budavari, S., Merck & Co., Inc., Rahway, NJ, p1304, 1989); Rebetol (Schering Plough) and Copegus (Roche). United States Patent No. 3,798,209 and RE29,835 disclose and claim ribavirin. Ribavirin is structurally similar to guanosine, and has in vitro activity against several DNA and RNA viruses including Flaviviridae (Gary L. Davis. *Gastroenterology* 118:S104-S114, 2000). U.S. Patent No 4,211,771 (to ICN Pharmaceuticals) discloses the use of ribavirin as an antiviral agent.

Ribavirin reduces serum amino transferase levels to normal in 40% of patients, but it does not lower serum levels of HCV-RNA (Gary L. Davis. *Gastroenterology* 118:S104-S114, 2000). Thus, ribavirin alone is not effective in reducing viral RNA levels. Additionally, ribavirin has significant toxicity and is known to induce anemia.

Interferons (IFNs) are compounds that have been commercially available for the treatment of chronic hepatitis for nearly a decade. IFNs are glycoproteins produced by immune cells in response to viral infection. IFNs inhibit viral replication of many viruses, including HCV, and when used as the sole treatment for hepatitis C infection, IFN suppresses serum HCV-RNA to undetectable levels. Additionally, IFN normalizes serum amino transferase levels. Unfortunately, the effects of IFN are temporary and a sustained response occurs in only 8%-9% of patients chronically infected with HCV (Gary L. Davis. *Gastroenterology* 118:S104-S114, 2000).

A number of patents disclose HCV treatments using interferon-based therapies. For example, U.S. Patent No. 5,980,884 to Blatt *et al.* discloses methods for retreatment of patients afflicted with HCV using consensus interferon. U.S. Patent No. 5,942,223 to Bazer *et al.* discloses an anti-HCV therapy using ovine or bovine interferon-tau. U.S. Patent No. 5,928,636 to Alber *et al.* discloses the combination therapy of interleukin-12 and interferon alpha for the treatment of infectious diseases including HCV. U.S. Patent No. 5,908,621 to Glue *et al.* discloses the use of polyethylene glycol modified interferon for the treatment of HCV. U.S. Patent No. 5,849,696 to Chretien *et al.* discloses the use of thymosins, alone or in combination with interferon, for treating HCV. U.S. Patent No. 5,830,455 to Valtuena *et al.* discloses a combination HCV therapy employing interferon and a free radical scavenger. U.S. Patent No. 5,738,845 to Imakawa discloses the use of human interferon tau proteins for treating HCV. Other interferon-based treatments for

HCV are disclosed in U.S. Patent No. 5,676,942 to Testa *et al.*, U.S. Patent No. 5,372,808 to Blatt *et al.*, and U.S. Patent No. 5,849,696.

Schering-Plough sells ribavirin as Rebetol® capsules (200 mg) for administration to patients with HCV. The U.S. FDA has approved Rebetol capsules to treat chronic HCV infection in combination with Schering's alpha interferon-2b products Intron® A and PEG-Intron™. Rebetol capsules are *not* approved for monotherapy (*i.e.*, administration independent of Intron®A or PEG-Intron), although Intron A and PEG-Intron are approved for monotherapy (*i.e.*, administration without ribavirin). Hoffman La Roche is selling ribavirin under the name CoPegus in Europe and the United States, also for use in combination with interferon for the treatment of HCV. Other alpha interferon products include Roferon-A (Hoffmann-La Roche), Infergen® (Intermune, formerly Amgen's product), and Wellferon® (Wellcome Foundation) are currently FDA-approved for HCV monotherapy. Interferon products currently in development for HCV include: Roferon-A (interferon alfa–2a) by Roche, PEGASYS (pegylated interferon alfa–2a) by Roche, INFERGEN (interferon alfacon-1) by InterMune, OMNIFERON (natural interferon) by Viragen, ALBUFERON by Human Genome Sciences, REBIF (interferon beta-1a) by Ares-Serono, Omega Interferon by BioMedicine, Oral Interferon Alpha by Amarillo Biosciences, and Interferon gamma-1b by InterMune.

The combination of IFN and ribavirin for the treatment of HCV infection has been reported to be effective in the treatment of IFN naïve patients (Battaglia, A.M. *et al.*, *Ann. Pharmacother.* 34:487-494, 2000). Combination treatment is effective both before hepatitis develops and when histological disease is present (Berenguer, M. *et al. Antivir. Ther.* 3(Suppl. 3):125-136, 1998). Currently, the most effective therapy for HCV is combination therapy of pegylated interferon with ribavirin (2002 NIH Consensus Development Conference on the Management of Hepatitis C). However, the side effects of combination therapy can be significant and include hemolysis, flu-like symptoms, anemia, and fatigue (Gary L. Davis. *Gastroenterology* 118:S104-S114, 2000).

(2) Substrate-based NS3 protease inhibitors (Attwood *et al.*, *Antiviral peptide derivatives*, PCT WO 98/22496, 1998; Attwood *et al.*, *Antiviral Chemistry and Chemotherapy* 1999, *10*, 259-273; Attwood *et al.*, *Preparation and use of amino acid derivatives as anti-viral agents,* German Patent Pub. DE 19914474; Tung *et al. Inhibitors of serine proteases, particularly hepatitis C virus NS3 protease*, PCT WO 98/17679),

including alphaketoamides and hydrazinoureas, and inhibitors that terminate in an electrophile such as a boronic acid or phosphonate (Llinas-Brunet et al., *Hepatitis C inhibitor peptide analogues,* PCT WO 99/07734).

(3) Non-substrate-based inhibitors such as 2,4,6-trihydroxy-3-nitro-benzamide derivatives (Sudo K. *et al., Biochemical and Biophysical Research Communications,* **1997,** *238,* 643-647; Sudo K. *et al. Antiviral Chemistry and Chemotherapy,* **1998,** *9,* 186), including RD3-4082 and RD3-4078, the former substituted on the amide with a 14 carbon chain and the latter processing a *para*-phenoxyphenyl group.

(4) Thiazolidine derivatives which show relevant inhibition in a reverse-phase HPLC assay with an NS3/4A fusion protein and NS5A/5B substrate (Sudo K. *et al., Antiviral Research,* **1996,** *32,* 9-18), especially compound RD-1-6250, possessing a fused cinnamoyl moiety substituted with a long alkyl chain, RD4 6205 and RD4 6193.

(5) Thiazolidines and benzanilides identified in Kakiuchi N. *et al. J. EBS Letters 421,* 217-220; Takeshita N. *et al. Analytical Biochemistry,* **1997,** *247,* 242-246.

(6) A phenan-threnequinone possessing activity against protease in a SDS-PAGE and autoradiography assay isolated from the fermentation culture broth of *Streptomyces* sp., Sch 68631 (Chu M. *et al., Tetrahedron Letters,* **1996,** *37,* 7229-7232), and Sch 351633, isolated from the fungus *Penicillium griscofuluum,* which demonstrates activity in a scintillation proximity assay (Chu M. *et al., Bioorganic and Medicinal Chemistry Letters 9,* 1949-1952).

(7) Selective NS3 inhibitors based on the macromolecule elgin c, isolated from leech (Qasim M.A. *et al., Biochemistry,* **1997,** *36,* 1598-1607).

(8) Helicase inhibitors (Diana G.D. *et al., Compounds, compositions and methods for treatment of hepatitis C,* U.S. Pat. No. 5,633,358; Diana G.D. *et al., Piperidine derivatives, pharmaceutical compositions thereof and their use in the treatment of hepatitis C,* PCT WO 97/36554).

(9) Polymerase inhibitors such as nucleotide analogues, gliotoxin (Ferrari R. *et al. Journal of Virology,* **1999,** *73,* 1649-1654), and the natural product cerulenin (Lohmann V. *et al., Virology,* **1998,** *249,* 108-118).

(10) Antisense phosphorothioate oligodeoxynucleotides (S-ODN) complementary to sequence stretches in the 5' non-coding region (NCR) of the virus (Alt M. *et al.,*

Hepatology, **1995**, *22*, 707-717), or nucleotides 326-348 comprising the 3' end of the NCR and nucleotides 371-388 located in the core coding region of the HCV RNA (Alt M. *et al.*, *Archives of Virology*, **1997**, *142*, 589-599; Galderisi U. *et al.*, *Journal of Cellular Physiology*, **1999**, *181*, 251-257).

(11) Inhibitors of IRES-dependent translation (Ikeda N *et al.*, *Agent for the prevention and treatment of hepatitis C*, Japanese Patent Pub. JP-08268890; Kai Y. *et al.* *Prevention and treatment of viral diseases*, Japanese Patent Pub. JP-10101591).

(12) Nuclease-resistant ribozymes (Maccjak, D. J. *et al.*, *Hepatology* **1999**, *30*, abstract 995).

(13) Nucleoside analogs have also been developed for the treatment of Flaviviridae infections.

Idenix Pharmaceuticals, Ltd. discloses branched nucleosides, and their use in the treatment of HCV and flaviviruses and pestiviruses in International Publication Nos. WO 01/90121 (filed May 23, 2001) and WO 01/92282 (filed May 26, 2001). A method for the treatment of hepatitis C infection (and flaviviruses and pestiviruses) in humans and other host animals is disclosed in the Idenix publications that includes administering an effective amount of a biologically active 1', 2', 3' or 4'-branched β-D or β-L nucleosides or a pharmaceutically acceptable salt or prodrug thereof, administered either alone or in combination, optionally in a pharmaceutically acceptable carrier.

WO 01/96353 (filed June 15, 2001) to Indenix Pharmaceuticals, Ltd. discloses 3'-prodrugs of 2'-deoxy-β-L-nucleosides for the treatment of HBV. U.S. Patent No. 4,957,924 to Beauchamp discloses various therapeutic esters of acyclovir.

Other patent applications disclosing the use of certain nucleoside analogs to treat hepatitis C virus include: PCT/CA00/01316 (WO 01/32153; filed November 3, 2000) and PCT/CA01/00197 (WO 01/60315; filed February 19, 2001) filed by BioChem Pharma, Inc. (now Shire Biochem, Inc.); PCT/US02/01531 (WO 02/057425; filed January 18, 2002) and PCT/US02/03086 (WO 02/057287; filed January 18, 2002) filed by Merck & Co., Inc., PCT/EP01/09633 (WO 02/18404; published August 21, 2001) filed by Roche, and PCT Publication No. WO 01/79246 (filed April 13, 2001) and WO 02/32920 (filed October 18, 2001) by Pharmasset.

(14) Other miscellaneous compounds including 1-amino-alkylcyclohexanes (U.S. Patent No. 6,034,134 to Gold *et al.*), alkyl lipids (U.S. Pat. No. 5,922,757 to Chojkier *et al.*), vitamin E and other antioxidants (U.S. Pat. No. 5,922,757 to Chojkier *et al.*), squalene, amantadine, bile acids (U.S. Pat. No. 5,846,964 to Ozeki *et al.*), N-(phosphonoacetyl)-L-aspartic acid, (U.S. Pat. No. 5,830,905 to Diana *et al.*), benzenedicarboxamides (U.S. Pat. No. 5,633,388 to Diana *et al.*), polyadenylic acid derivatives (U.S. Pat. No. 5,496,546 to Wang *et al.*), 2',3'-dideoxyinosine (U.S. Pat. No. 5,026,687 to Yarchoan *et al.*), and benzimidazoles (U.S. Pat. No. 5,891,874 to Colacino *et al.*).

(15) Other compounds currently in clinical development for treatment of hepatitis c virus include: Interleukin-10 by Schering-Plough, IP-501 by Interneuron, Merimebodib VX-497 by Vertex, AMANTADINE (Symmetrel) by Endo Labs Solvay, HEPTAZYME by RPI, IDN-6556 by Idun Pharma., XTL-002 by XTL., HCV/MF59 by Chiron, CIVACIR by NABI, LEVOVIRIN by ICN, VIRAMIDINE by ICN, ZADAXIN (thymosin alfa-1) by Sci Clone, CEPLENE (histamine dihydrochloride) by Maxim, VX 950 / LY 570310 by Vertex/Eli Lilly, ISIS 14803 by Isis Pharmaceutical/Elan, IDN-6556 by Idun Pharmaceuticals, Inc. and JTK 003 by AKROS Pharma.

U.S. Patent No. 6,348,587 to Emory University and the University of Georgia Research Foundation discloses the use of 2'-fluoronucleosides for the treatment of HIV, hepatitis B, hepatitis C and abnormal cellular proliferation.

Abnormal Cellular Proliferation

Cellular differentiation, growth, function and death are regulated by a complex network of mechanisms at the molecular level in a multicellular organism. In the healthy animal or human, these mechanisms allow the cell to carry out its designed function and then die at a programmed rate.

Abnormal cellular proliferation, notably hyperproliferation, can occur as a result of a wide variety of factors, including genetic mutation, infection, exposure to toxins, autoimmune disorders, and benign or malignant tumor induction.

There are a number of skin disorders associated with cellular hyperproliferation. Psoriasis, for example, is a benign disease of human skin generally characterized by plaques covered by thickened scales. The disease is caused by increased proliferation of epidermal cells of unknown cause. In normal skin the time required for a cell to move from the basal layer to the upper granular layer is about five weeks. In psoriasis, this time is only 6 to 9 days, partially due to an increase in the number of proliferating cells and an increase in the proportion of cells which are dividing (G. Grove, Int. J. Dermatol. 18:111, 1979). Approximately 2% of the population in the United States have psoriasis, occurring in about 3% of Caucasian Americans, in about 1% of African Americans, and rarely in native Americans. Chronic eczema is also associated with significant hyperproliferation of the epidermis. Other diseases caused by hyperproliferation of skin cells include atopic dermatitis, lichen planus, warts, pemphigus vulgaris, actinic keratosis, basal cell carcinoma and squamous cell carcinoma.

Other hyperproliferative cell disorders include blood vessel proliferation disorders, fibrotic disorders, autoimmune disorders, graft-versus-host rejection, tumors and cancers.

Blood vessel proliferative disorders include angiogenic and vasculogenic disorders. Proliferation of smooth muscle cells in the course of development of plaques in vascular tissue cause, for example, restenosis, retinopathies and atherosclerosis. The advanced lesions of atherosclerosis result from an excessive inflammatory-proliferative response to an insult to the endothelium and smooth muscle of the artery wall (Ross, R. Nature, **1993**, 362:801-809). Both cell migration and cell proliferation play a role in the formation of atherosclerotic lesions.

Fibrotic disorders are often due to the abnormal formation of an extracellular matrix. Examples of fibrotic disorders include hepatic cirrhosis and mesangial proliferative cell disorders. Hepatic cirrhosis is characterized by the increase in extracellular matrix constituents resulting in the formation of a hepatic scar. Hepatic cirrhosis can cause diseases such as cirrhosis of the liver. An increased extracellular matrix resulting in a hepatic scar can also be caused by viral infection such as hepatitis. Lipocytes appear to play a major role in hepatic cirrhosis.

Mesangial disorders are brought about by abnormal proliferation of mesangial cells. Mesangial hyperproliferative cell disorders include various human renal diseases,

such as glomerulonephritis, diabetic nephropathy, malignant nephrosclerosis, thrombotic micro-angiopathy syndromes, transplant rejection, and glomerulopathies.

Another disease with a proliferative component is rheumatoid arthritis. Rheumatoid arthritis is generally considered an autoimmune disease that is thought to be associated with activity of autoreactive T cells (See, e.g., Harris, E. D., Jr., The New England Journal of Medicine, **1990**, 322: 1277-1289), and to be caused by autoantibodies produced against collagen and IgE.

Other disorders that can include an abnormal cellular proliferative component include Behcet's syndrome, acute respiratory distress syndrome (ARDS), ischemic heart disease, post-dialysis syndrome, leukemia, acquired immune deficiency syndrome, vasculitis, lipid histiocytosis, septic shock and inflammation in general.

A tumor, also called a neoplasm, is a new growth of tissue in which the multiplication of cells is uncontrolled and progressive. A benign tumor is one that lacks the properties of invasion and metastasis and is usually surrounded by a fibrous capsule. A malignant tumor (i.e., cancer) is one that is capable of both invasion and metastasis. Malignant tumors also show a greater degree of anaplasia (i.e., loss of differentiation of cells and of their orientation to one another and to their axial framework) than benign tumors.

Approximately 1.2 million Americans are diagnosed with cancer each year, 8,000 of which are children. In addition, 500,000 Americans die from cancer each year in the United States alone. Prostate and lung cancers are the leading causes of death in men while breast and lung cancer are the leading causes of death in women. It is estimated that cancer-related costs account for about 10 percent of the total amount spent on disease treatment in the United States (CNN.Cancer.Facts: http://www.cnn.com/HEALTH/9511/conquer_cancer/facts/ index.html, page 2 of 2, July 18, 1999).

In view of the severity of diseases associated with *Flaviviridae* infection and/or abnormally proliferating cells, including cancer, and their pervasiveness in animals, including humans, it is an object of the present invention to provide a compound, method and composition for the treatment of a host, including animals and especially humans, with a disease associated with a *Flaviviridae* infection and/or abnormally proliferating cells.

It is a particular object of the present invention to provide a compound, method and composition for the treatment of a host, including animals and especially humans, infected with a *Flaviviridae* virus.

It is a further object to provide a compound, method and composition for the treatment of a host, including animals and especially humans, infected with hepatitis C virus.

It is another object of the present invention to provide a compound, method and composition for the treatment of a host, including animals and especially humans, with abnormal cellular proliferation.

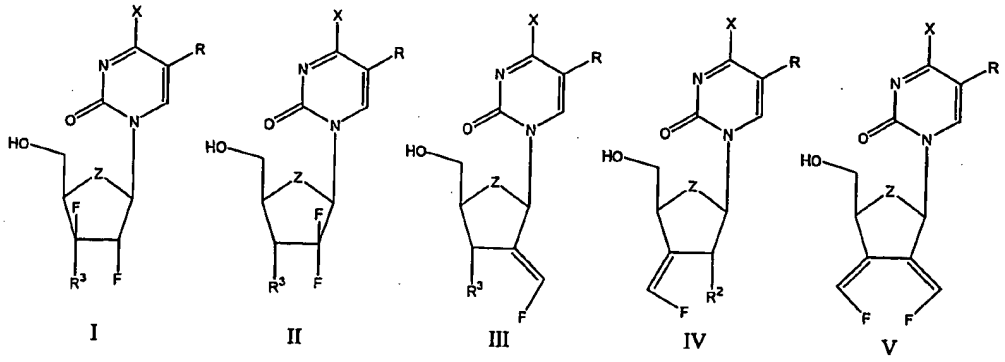
It is yet another object to provide a compound, method and composition for the treatment of a host, including animals and especially humans, with a malignant tumor.

SUMMARY OF THE INVENTION

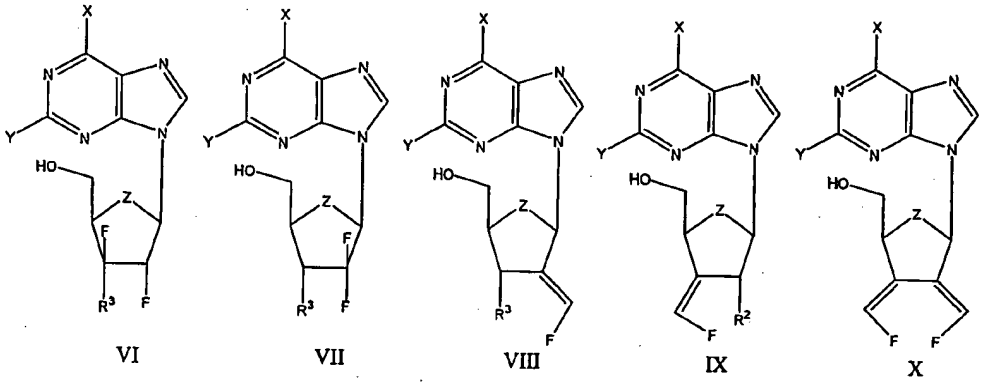
The present invention is a β-D or β-L nucleoside of the formula **(I)** – **(XX)**, or its pharmaceutically acceptable salt or prodrug, and the use of such compounds for the treatment of a host infected with a virus belonging to the *Flaviviridae* family. The invention also includes a method for treating a *Flaviviridae* infection, including an HCV infection, that includes the administration of an anti-viral effective amount of a β-D or β-L nucleoside of the formula **(I)** – **(XX)**, or its pharmaceutically acceptable salt or prodrug, optionally in a pharmaceutically acceptable carrier or diluent, optionally in combination or alternation with another effective antiviral agent.

Alternatively, a β-D or β-L nucleoside of the formula **(I)-(XX)**, and in particular, **(III)** – **(V)** or **(VIII)** - **(X)**, or its pharmaceutically acceptable salt or prodrug thereof, can be used for the treatment of abnormal cellular proliferation. The invention also includes a method for treating abnormal cellular proliferation, including a malignant tumor, that includes the administration of an anti-proliferatively effective amount of a β-D or β-L nucleoside of the formula **(I)** – **(XX)**, or its pharmaceutically acceptable salt or prodrug, optionally in a pharmaceutically acceptable carrier or diluent, optionally in combination or alternation with another effective antiproliferative agent.

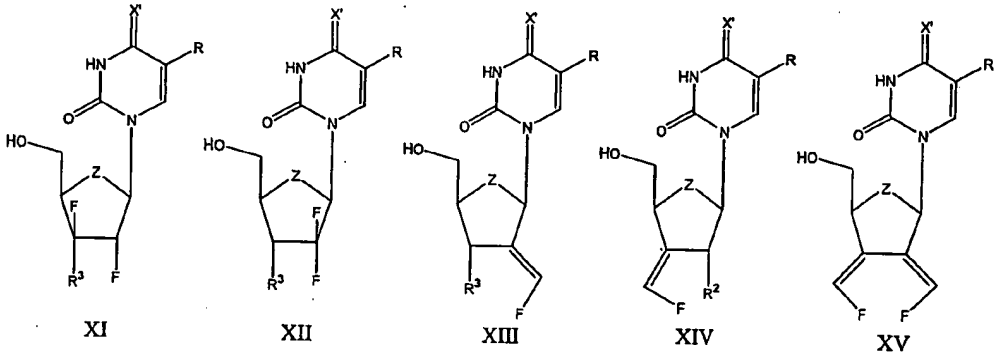
In one embodiment of the present invention, the nucleoside is a β-D or β-L nucleoside of the general formula (I) - (XX):



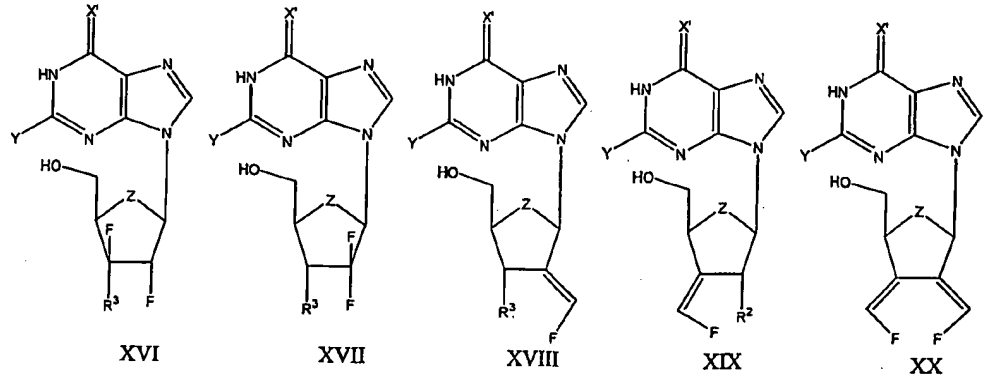
I II III IV V



VI VII VIII IX X



XI XII XIII XIV XV



XVI XVII XVIII XIX XX

or its pharmaceutically acceptable salt or prodrug thereof, wherein:

(a) R is H, halogen (F, Cl, Br, I), OH, OR', SH, SR', NH_2, NHR', NR'$_2$, lower alkyl of C_1-C_6, halogenated (F, Cl, Br, I) lower alkyl of C_1-C_6 such as CF_3 and CH_2CH_2F, lower alkenyl of C_2-C_6 such as $CH=CH_2$, halogenated (F, Cl, Br, I) lower alkenyl of C_2-C_6 such as CH=CHCl, CH=CHBr and CH=CHI, lower alkynyl of C_2-C_6 such as C≡CH, halogenated (F, Cl, Br, I) lower alkynyl of C_2-C_6, lower alkoxy of C_1-C_6 such as CH_2OH and CH_2CH_2OH, CO_2H, CO_2R', $CONH_2$, CONHR', CONR'$_2$, $CH=CHCO_2H$, $CH=CHCO_2R'$;

(b) X and Y are independently H, halogen, OH, OR', OCH_3, SH, SR', SCH_3, NH_2, NHR', NR'$_2$, CH_3;

(c) each R' is independently a hydrogen, acyl, lower alkyl of C_1-C_6 or lower cycloalkyl of C_1-C_6;

(d) Z is O, S or CH_2;

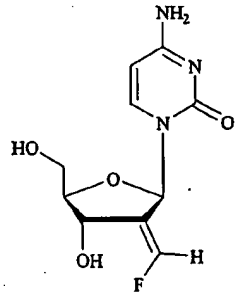
(e) R^2 is F or OH;

(f) R^3 is F or OH; and

(g) X' is O, S, NH, NR', CH_2, or CHR';

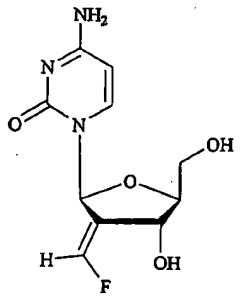
(h) with the proviso for compound II that when X is NH_2 or compound XII when X is NH and R is H, then R^3 is not OH.

In one embodiment of the present invention, a β-D nucleoside of the formula:



or its pharmaceutically acceptable salt or prodrug thereof, is provided for the treatment or prophylaxis of a *Flaviviridae* infection, and in particular HCV.

In yet another particular embodiment of the present invention, a β-L nucleoside of the formula:



or its pharmaceutically acceptable salt or prodrug thereof, is provided for the treatment or prophylaxis of a disease associated with abnormal cellular proliferation, and in particular a malignant tumor.

In one embodiment of the invention, the nucleoside of the invention is the isolated β-D or β-L isomer. In another embodiment of the invention, the nucleosides are enantiomerically enriched. In yet another embodiment of the invention, the nucleosides is in a enantiomeric mixture in which the desired enantiomer is at least 95%, 98% or 99% pure or free of its corresponding enantiomer.

In another embodiment, the nucleoside has an EC_{50} (effective concentration to achieve 50% inhibition) when tested in an appropriate cell-based assay, of less than 15 micromolar, and more particularly, less than 10 or 5 micromolar.

Specifically, the invention also includes methods for treating or preventing *Flaviviridae* infection, including all members of the Hepacivirus genus (HCV), Pestivirus genus (BVDV, CSFV, BDV), or Flavivirus genus (Dengue virus, Japanese encephalitis virus group (including West Nile Virus), and Yellow Fever virus); and abnormal cellular proliferation, including malignant tumors.

The present invention also includes at least the following features:

(a) β-D and β-L nucleosides of the general formula (**I**) - (**XX**), or their pharmaceutically acceptable salts or prodrugs thereof, as described herein;

(b) processes for the preparation of the β-D and β-L nucleosides of the general formula (**I**) - (**XX**), or their pharmaceutically acceptable salts or prodrugs thereof, as described herein;

(c) pharmaceutical compositions comprising a β-D or β-L nucleoside of the general formula (I) - (XX), or its pharmaceutically acceptable salt or prodrug thereof, in a pharmaceutically acceptable carrier or diluent thereof, as described herein, for the treatment or prophylaxis of a *Flaviviridae* infection in a host;

(d) pharmaceutical compositions comprising a β-D or β-L nucleoside of the general formula (I) - (XX), or its pharmaceutically acceptable salt or prodrug thereof, in combination with one or more other effective antiviral agent(s), optionally in a pharmaceutically acceptable carrier or diluent thereof, as described herein, for the treatment or prophylaxis of a *Flaviviridae* infection in a host;

(e) methods for the treatment or prophylaxis of a *Flaviviridae* infection in a host comprising administering an effective amount of a β-D or β-L nucleoside of the general formula (I) - (XX), or its pharmaceutically acceptable salt or prodrug thereof, optionally in a pharmaceutically acceptable carrier or diluent thereof, as described herein;

(f) methods for the treatment or prophylaxis of a *Flaviviridae* infection in a host comprising administering an effective amount of a β-D or β-L nucleoside of the general formula (I) - (XX), or its pharmaceutically acceptable salt or prodrug thereof, in combination or alternation with one or more other effective antiviral agent(s), optionally in a pharmaceutically acceptable carrier or diluent thereof, as described herein;

(g) use of a β-D or β-L nucleoside of the general formula (I) - (XX), or its pharmaceutically acceptable salt or prodrug thereof, optionally in a pharmaceutically acceptable carrier, as described herein, for the treatment or prophylaxis of a *Flaviviridae* infection in a host;

(h) use of a β-D or β-L nucleoside of the general formula (I) - (XX), or its pharmaceutically acceptable salt or prodrug thereof, in combination or alternation with one or more other effective antiviral agent(s), optionally in a pharmaceutically acceptable carrier, as described herein, for the treatment or prophylaxis of a *Flaviviridae* infection in a host;

(i) use of a β-D or β-L nucleoside of the general formula (I) - (XX), or its pharmaceutically acceptable salt or prodrug thereof, optionally in a pharmaceutically

acceptable carrier, as described herein, in the manufacture of a medicament for the treatment or prophylaxis of a *Flaviviridae* infection in a host;

(j) use of a β-D or β-L nucleoside of the general formula (I) - (XX), or its pharmaceutically acceptable salt or prodrug thereof, in combination or alternation with one or more other effective antiviral agent(s), optionally in a pharmaceutically acceptable carrier, as described herein, in the manufacture of a medicament for the treatment or prophylaxis of a *Flaviviridae* infection in a host;

(k) use of a β-D or β-L nucleoside of the general formula (I) - (XX), as described herein, or its pharmaceutically acceptable salt or prodrug thereof, optionally in a pharmaceutically acceptable carrier or diluent, as described herein, in a medical therapy, i.e. as antiviral or antitumor/anticancer agent, for example for the treatment or prophylaxis of a *Flaviviridae* infections, including hepatitis C infection or abnormal cellular proliferation, including a malignant tumor, in a host;

(l) use of a β-D or β-L nucleoside of the general formula (I) - (XX), as described herein, or its pharmaceutically acceptable salt or prodrug thereof, i.e. as antiviral or antitumor/anticancer agent, in combination or alternation with one or more other effective therapeutic agent(s), i.e. another antiviral or antitumor/anticancer agent, optionally in a pharmaceutically acceptable carrier or diluent, as described herein, in a medical therapy, for example for the treatment or prophylaxis of a *Flaviviridae* infections, including hepatitis C infection or abnormal cellular proliferation, including a malignant tumor, in a host;

(m) pharmaceutical compositions comprising a β-D or β-L nucleoside of the general formula (I) - (XX), or its pharmaceutically acceptable salt or prodrug thereof, in a pharmaceutically acceptable carrier or diluent thereof, as described herein, for the treatment or prophylaxis of a disease associated with abnormal cellular proliferation in a host;

(n) pharmaceutical compositions comprising a β-D or β-L nucleoside of the general formula (I) - (XX), or its pharmaceutically acceptable salt or prodrug thereof, in combination with one or more other effective antiviral agent(s), optionally in a pharmaceutically acceptable carrier or diluent thereof, as described herein, for the treatment or prophylaxis of a disease associated with abnormal cellular proliferation in a host;

(o) methods for the treatment or prophylaxis of a disease associated with abnormal cellular proliferation in a host comprising administering an effective amount of a β-D or β-L nucleoside of the general formula (I) - (XX), or its pharmaceutically acceptable salt or prodrug thereof, optionally in a pharmaceutically acceptable carrier or diluent thereof, as described herein;

(p) methods for the treatment or prophylaxis of a disease associated with abnormal cellular proliferation in a host comprising administering an effective amount of a β-D or β-L nucleoside of the general formula (I) - (XX), or its pharmaceutically acceptable salt or prodrug thereof, in combination or alternation with one or more other effective antiviral agent(s), optionally in a pharmaceutically acceptable carrier or diluent thereof, as described herein;

(q) use of a β-D or β-L nucleoside of the general formula (I) - (XX), or its pharmaceutically acceptable salt or prodrug thereof, optionally in a pharmaceutically acceptable carrier, as described herein, for the treatment or prophylaxis of a disease associated with abnormal cellular proliferation in a host;

(r) use of a β-D or β-L nucleoside of the general formula (I) - (XX), or its pharmaceutically acceptable salt or prodrug thereof, in combination or alternation with one or more other effective antiviral agent(s), optionally in a pharmaceutically acceptable carrier, as described herein, for the treatment or prophylaxis of a disease associated with abnormal cellular proliferation in a host;

(s) use of a β-D or β-L nucleoside of the general formula (I) - (XX), or its pharmaceutically acceptable salt or prodrug thereof, optionally in a pharmaceutically acceptable carrier, as described herein, in the manufacture of a medicament for the treatment or prophylaxis of a disease associated with abnormal cellular proliferation in a host; and

(t) use of a β-D or β-L nucleoside of the general formula (I) - (XX), or its pharmaceutically acceptable salt or prodrug thereof, in combination or alternation with one or more other effective antiviral agent(s), optionally in a pharmaceutically acceptable carrier, as described herein, in the manufacture of a medicament for the treatment or prophylaxis of a disease associated with abnormal cellular proliferation in a host.

BRIEF DESCRIPTION OF THE FIGURES

Figure 1 is a graphical depiction of the dose-dependant reduction of the replicon HCV RNA based on treatment with Gemcitabine (♦: ΔCt for HCV RNA). This viral reduction was compared to the reduction of cellular DNA levels (ribosomal DNA) or cellular RNA levels (ribosomal RNA) to obtain the therapeutic index ΔΔCt values (▲: HCV-rDNA ΔΔCt; **X:** HCV-rRNA ΔΔCt).

Figure 2 is a graphical depiction of the dose-dependant reduction of the replicon HCV RNA based on treatment with 2'-deoxy-2'-fluorocytidine (♦: ΔCt for HCV RNA). This viral reduction was compared to the reduction of cellular DNA levels (ribosomal DNA) or cellular RNA levels (ribosomal RNA) to obtain the therapeutic index ΔΔCt values (▲: HCV-rDNA ΔΔCt; **X:** HCV-rRNA ΔΔCt).

DETAILED DESCRIPTION OF THE INVENTION

The invention is a β-D or β-L nucleoside of the formula **(I)** – **(XX)**, or its pharmaceutically acceptable salt or prodrug and the use of such compounds for the treatment of a host infected with a virus belonging to the *Flaviviridae* family. The invention also includes a method for treating a *Flaviviridae* infection, including an HCV infection, that includes the administration of an anti-viral effective amount of a β-D or β-L nucleoside of the formula (I) - (XX), or its pharmaceutically acceptable salt or prodrug, optionally in a pharmaceutically acceptable carrier or diluent, optionally in combination or alternation with another effective antiviral agent.

Alternatively, a β-L nucleoside of the formula (I) – (XX), or its pharmaceutically acceptable salt or prodrug thereof, can be used for the treatment of abnormal cellular proliferation. The invention also includes a method for treating abnormal cellular proliferation, including a malignant tumor, that includes the administration of an anti-proliferatively effective amount of a β-L nucleoside of the formula **(I)** – **(XX)**, or its pharmaceutically acceptable salt or prodrug, optionally in a pharmaceutically acceptable carrier or diluent, optionally in combination or alternation with another effective antiproliferative agent.

Specifically, the invention also includes methods for treating or preventing *Flaviviridae* infection, including all members of the Hepacivirus genus (HCV), Pestivirus genus (BVDV, CSFV, BDV), or Flavivirus genus (Dengue virus, Japanese encephalitis virus group (including West Nile Virus), and Yellow Fever virus); and abnormal cellular proliferation, including malignant tumors.

In an additional embodiment, a method for the treatment or prophylaxis of a mammal having a virus-associated disorder which comprises administering to the mammal a pharmaceutically effective amount of a β-D or β-L nucleoside of the general formula (I) – (XX), or its pharmaceutically acceptable salt or prodrug optionally in a combination or alternation with one or more other anti-viral effective agent(s), optionally in a pharmaceutically acceptable carrier or diluent, as disclosed herein, is provided. In a preferred embodiment, the mammal is a human.

In another embodiment, the use of a β-D or β-L nucleoside of the general formula (I) – (XX), or its pharmaceutically acceptable salt or prodrug optionally in a combination or alternation with one or more other anti-viral effective agent(s), optionally in a pharmaceutically acceptable carrier or diluent, as disclosed herein, for the treatment or prophylaxis of a mammal having a virus-associated disorder is provided. In a preferred embodiment, the mammal is a human.

In an additional embodiment, a method for the treatment or prophylaxis of a mammal having a disorder associated with abnormal cellular proliferation which comprises administering to the mammal a pharmaceutically effective amount of a β-D or β-L nucleoside of the general formula (III) - (V) or (VIII) - (X), or its pharmaceutically acceptable salt or prodrug optionally in a combination or alternation with one or more other anti-proliferatively effective agent(s), optionally in a pharmaceutically acceptable carrier or diluent, as disclosed herein, is provided. In a preferred embodiment, the mammal is a human.

In another embodiment, the use of a β-D or β-L nucleoside of the general formula (I) - (XX), or its pharmaceutically acceptable salt or prodrug thereof, optionally in a combination or alternation with one or more other anti-proliferatively effective agent(s), optionally in a pharmaceutically acceptable carrier or diluent, as disclosed herein, for the treatment or prophylaxis of a mammal having a disorder associated with abnormal cellular proliferation is provided. In a preferred embodiment, the mammal is a human.

The *Flaviviridaeviruses* that can be treated include Flaviviruses, including the Dengue virus group (Dengue virus, Dengue virus type 1, Dengue virus type 2, Dengue virus type 3, Dengue virus type 4), the Japanese encephalitis virus group (Alfuy Virus, Japanese encephalitis virus, Kookaburra virus, Koutango virus, Kunjin virus, Murray Valley encephalitis virus, St. Louis encephalitis virus, Stratford virus, Usutu virus, West Nile Virus), the Modoc virus group, the Rio Bravo virus group (Apoi virus, Rio Brovo virus, Saboya virus), the Ntaya virus group, the Tick-Borne encephalitis group (tick born encephalitis virus), the Tyuleniy virus group, Uganda S virus group and the Yellow Fever virus group; Pestiviruses, including Bovine Viral Diarrhea Virus-2 (BVDV-2), Pestivirus type 1 (including BVDV), Pestivirus type 2 (including Hog Cholera Virus) and Pestivirus type 3 (including Border Disease Virus), and Hepaciviruses, including hepatitis C virus (HCV), which is composed of many clades, types and subtypes.

I. Disorders Characterized by Abnormal Cellular Proliferation

Non-limiting examples of proliferative disorders that can be treated and/or imaged with a compound or composition of the present invention include those in **Table 1**, as well as any others listed or described in the Background of the Invention or otherwise in the specification.

Table 1

Organ System	Disease/Pathology
Dermatological	Psoriasis (all forms), acne vulgaris, acne rosacea, common warts, anogenital (venereal) warts, eczema; lupus associated skin lesions; dermatitides such as seborrheic dermatitis and solar dermatitis; keratoses such as seborrheic keratosis, senile keratosis, actinic keratosis, photo-induced keratosis, skin aging, including photo-induced skin aging, keratosis follicularis, keloids and Prophylaxis against keloid formation; leukoplakia, lichen, planus, keratitis, contact dermatitis, eczema, urticaria, pruritus, hidradenitis, acne inversa
Cardiovascular	Hypertension, vasculo-occlusive diseases including Atherosclerosis, thrombosis and restenosis after angioplasty; acute coronary syndromes such as unstable angina, myocardial infarction, ischemic and non-ischemic cardiomyopathies, post-MI cardiomyopathy and myocardial fibrosis, substance-induced cardiomyopathy.
Endocrine	Insulin resistant states including obesity, diabetes mellitus (types 1 & 2), diabetic retinopathy, macular degeneration associated with diabetes, gestational diabetes, impaired glucose tolerance, polycystic ovarian syndrome; osteoporosis, osteopenia, accelerated aging of tissues and organs including Werner's syndrome.
Urogenital	Endometriosis, benign prostatic hyperplasia, leiomyoma, Polycystic kidney disease, diabetic nephropathy.
Pulmonary	Asthma, chronic obstructive pulmonary disease (COPD), reactive Airway disease, pulmonary fibrosis, pulmonary hypertension.

Organ System	Disease/Pathology
Connective tissue/joints	Immunological Rheumatoid arthritis, Raynaud's phenomenon/disease, Sjogren's Syndrome, systemic sclerosis, systemic lupus erythematosus, vasculitides, ankylosing spondylitis, osteoarthritis, reactive arthritis, psoriatic arthritis, fibromyalgia.
Other	Fibrocystic breast disease, fibroadenoma, chronic fatigue syndrome.

Nonlimiting examples of neoplastic diseases or malignancies treatable and/or diagnosable with a compound or composition of the present invention are listed in **Table 2.**

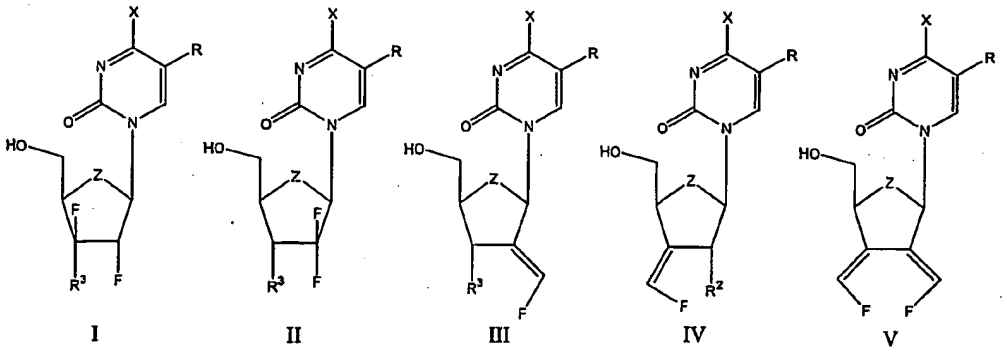
Table 2

Organ System	Malignancy/Cancer type
Skin	Basal cell carcinoma, melanoma, squamous cell carcinoma; cutaneous T cell lymphoma; Kaposi's sarcoma.
Hematological	Acute leukemia, chronic leukemia and myelodysplastic syndromes.
Urogenital	Prostatic, renal and bladder carcinomas, anogenital carcinomas including cervical, ovarian, uterine, vulvar, vaginal, and those associated with human papilloma virus infection.
Neurological	Gliomas including glioblastomas, astrocytoma, ependymoma, medulloblastoma, oligodendroma; meningioma, pituitary adenoma, neuroblastoma, craniopharyngioma.
Gastrointestinal	Colon, colorectal, gastric, esophageal, mucocutaneous carcinomas.
Breast	Breast cancer including estrogen receptor and progesterone Receptor positive or negative subtypes, soft tissue tumors.

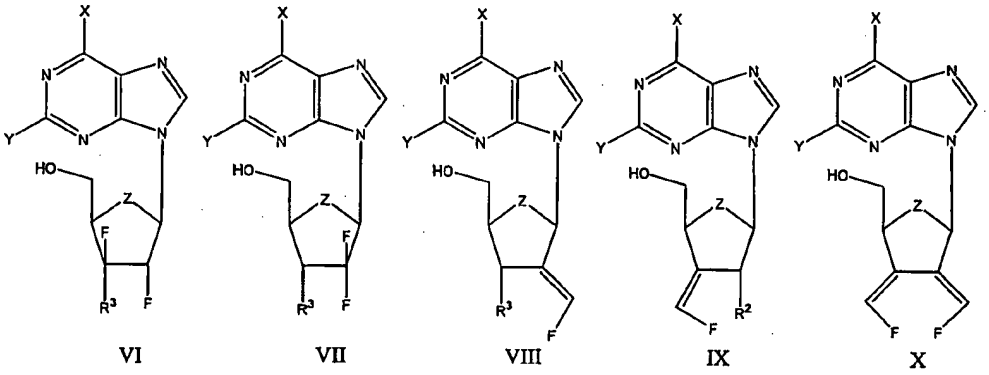
Organ System	Malignancy/Cancer type
Metastasis	Metastases resulting from the neoplasms.
Skeletal	Osteogenic sarcoma, malignant fibrou histeocytoma, chondrosarcoma, rhabdomyosarcoma, leiomyosarcoma, myeloma.
Diffuse Tumors	Lymphoma (non-Hodgkin's or Hodgkin's), sickle cell anemia.
Other	Angiomata, angiogenesis associated with the neoplasms.

II. Compounds of the Invention

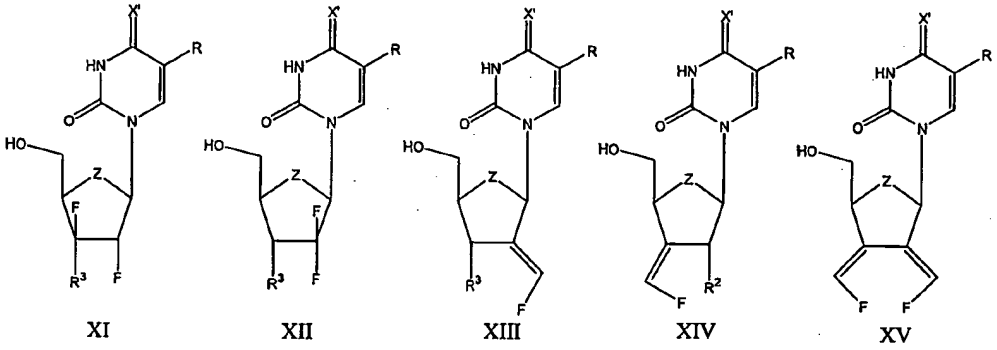
In one embodiment, the nucleoside is a β-D or β-L nucleoside of the general formula (I) - (XX):



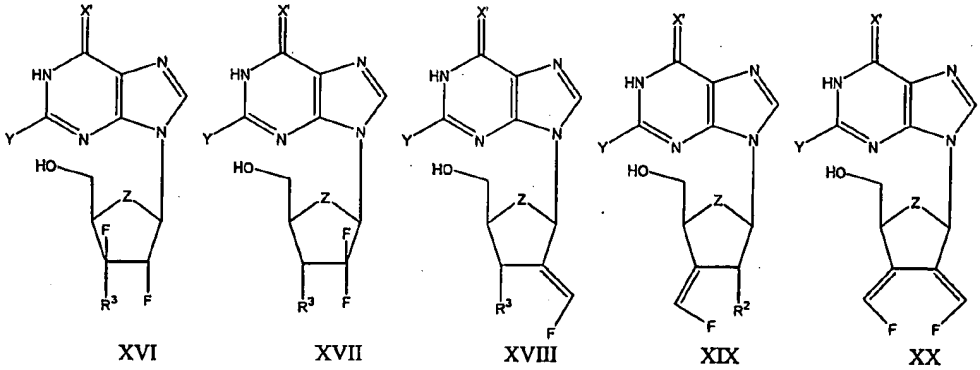
I II III IV V



VI VII VIII IX X



XI XII XIII XIV XV



XVI XVII XVIII XIX XX

or its pharmaceutically acceptable salt or prodrug thereof, or its use as further described herein wherein:

(a) R is H, halogen (F, Cl, Br, I), OH, OR', SH, SR', NH_2, NHR', NR'$_2$, lower alkyl of C_1-C_6, halogenated (F, Cl, Br, I) lower alkyl of C_1-C_6 such as CF_3 and CH_2CH_2F, lower alkenyl of C_2-C_6 such as $CH=CH_2$, halogenated (F, Cl, Br, I) lower alkenyl of C_2-C_6 such as CH=CHCl, CH=CHBr and CH=CHI, lower alkynyl of C_2-C_6 such as C≡CH, halogenated (F, Cl, Br, I) lower alkynyl of C_2-C_6, lower alkoxy of C_1-C_6 such as CH_2OH and CH_2CH_2OH, CO_2H, CO_2R', $CONH_2$, CONHR', CONR'$_2$, $CH=CHCO_2H$, $CH=CHCO_2R'$;

(b) X and Y are independently H, halogen, OH, OR', OCH_3, SH, SR', SCH_3, NH_2, NHR', NR'$_2$, CH_3;

(c) each R' is independently a hydrogen, acyl, lower alkyl of C_1-C_6 or lower cycloalkyl of C_1-C_6;

(d) Z is O, S or CH_2;

(e) R^2 is F or OH;

(f) R^3 is F or OH; and

(g) X' is O, S, NH, NR', CH_2, or CHR';

(h) with the proviso for compound II that when X is NH_2 or compound XII when X is NH and R is H, then R^3 is not OH.

In one embodiment, the fluorinated derivatives are preferred.

In another embodiment, the *gem*-difluoro-nucleosides are preferred.

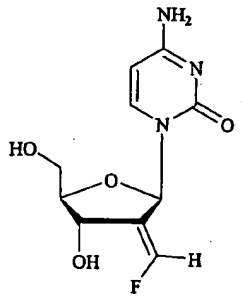
In an important embodiment, none of the aspects of the invention include gemcitabine (β-D-2',2'-difuoro-2'deoxycytidine).

In yet another embodiment, the 2'-(fluoromethylidene) and/or 3'-(fluoromethylidene) nucleosides, the vinylogous analogs of 2'-fluoro-2'-deoxy nucleosides, are preferred. In particular, E configuration is preferred.

The present invention provides a β-D or β-L nucleosides of the formula (**I**) – (**XX**), or its pharmaceutically acceptable salt or prodrug and the use of such compounds for the treatment of a host infected with a virus belonging to the *Flaviviridae* family, as well as β-L nucleoside of the formula (**I**) – (**XX**), or its pharmaceutically acceptable salt or prodrug

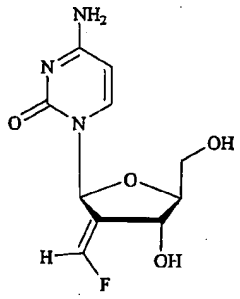
thereof, and the use of such compounds are provided for the treatment of abnormal cellular proliferation.

In yet another particular embodiment of the present invention, a β-D nucleoside of the formula:



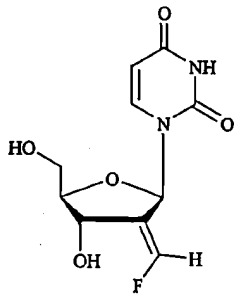
or its pharmaceutically acceptable salt or prodrug thereof, is provided for the treatment or prophylaxis of a *Flaviviridae* infection, and in particular HCV.

In yet another particular embodiment of the present invention, a β-L nucleoside of the formula:



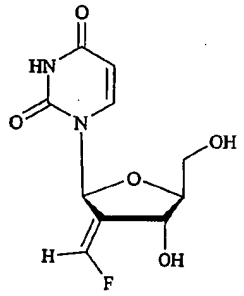
or its pharmaceutically acceptable salt or prodrug thereof, is provided for the treatment or prophylaxis of a disease associated with abnormal cellular proliferation, and in particular a malignant tumor.

In yet another particular embodiment of the present invention, a β-D nucleoside of the formula:



or its pharmaceutically acceptable salt or prodrug thereof, is provided for the treatment or prophylaxis of a *Flaviviridae* infection, and in particular HCV.

In yet another particular embodiment of the present invention, a β-L nucleoside of the formula:



or its pharmaceutically acceptable salt or prodrug thereof, is provided for the treatment or prophylaxis of a disease associated with abnormal cellular proliferation, and in particular a malignant tumor.

In yet another embodiment, the nucleoside is a β-D or β-L nucleoside of the general formula (I) - (XX):